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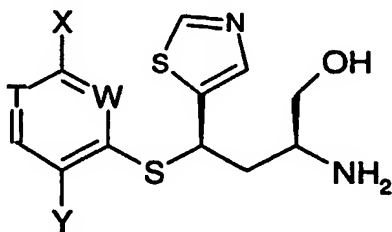
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ning of each regular issue of the PCT Gazette.

(54) Title: ANTIINFLAMMATORY 3-ARYLTHIO-3-THIAZOLYL-ALKYLAMINES



(I)

(57) Abstract: There are provided novel compounds of formula (I) wherein  
T, X, Y and W are as defined in the specification, and pharmaceutically ac-  
ceptable salts thereof, and enantiomers and racemates thereof; together with  
processes for their preparation, compositions containing them and their use in  
therapy. The compounds are inhibitors of nitric oxide synthase and are thereby  
particularly useful in the treatment or prophylaxis of inflammatory disease and  
pain.

## Antiinflammatory 3-arylthio-3-thiazolyl-alkylamines.

### Field of the Invention

- 5 The present invention relates to novel arylthiazolylthioalkylamine derivatives, processes for their preparation, compositions containing them and their use in therapy.

### Background of the Invention

- 10 Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure  
15 and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been particularly implicated in the pathogenesis of inflammatory diseases. Regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states (J. E. Macdonald, *Ann. Rep. Med. Chem.*, 1996, 31, 221 - 230).  
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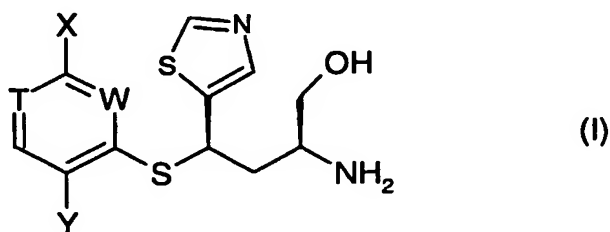
Considerable effort has been expended in efforts to identify compounds that act as specific inhibitors of one or more isoforms of the enzyme nitric oxide synthase. The use of such compounds in therapy has also been widely claimed.

25

- Patent application WO 02/090332 discloses certain arylheteroalkylamine derivatives that are useful as NOS inhibitors. It has now been found that certain compounds that are within the generic scope of this application, but which are not specifically exemplified therein, possess surprisingly advantageous properties. These compounds are the subject of the  
30 present application.

Disclosure of the invention

According to the present invention, there is provided a compound of formula (I)



wherein:

T and W independently represent CR<sup>1</sup> or N; and when more than one R<sup>1</sup> group is present, each may be selected independently;

X and R<sup>1</sup> independently represent H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO<sub>2</sub>, CHO, COCH<sub>3</sub> or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

Y represents C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO<sub>2</sub>, CHO, COCH<sub>3</sub> or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

or a pharmaceutically acceptable salt thereof.

In one embodiment, Y represents CN or halogen.

In one embodiment, X and R<sup>1</sup> independently represent H, halogen or CF<sub>3</sub>.

The compounds of formula (I) and their pharmaceutically acceptable salts have the advantage that they are inhibitors of the enzyme nitric oxide synthase (NOS). In particular, the

compounds of formula (I) and their pharmaceutically acceptable salts have the advantage that they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase (iNOS).

5 The invention further provides a process for the preparation of compounds of formula (I) or a pharmaceutically acceptable salt, enantiomer or racemate thereof.

According to the invention there is also provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

10 Another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

15 A more particular aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

20 According to the invention, there is also provided a method of treating, or reducing the risk of, diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

25 More particularly, there is also provided a method of treating, or reducing the risk of, inflammatory disease in a person suffering from or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

30 The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance; particularly in combination with a cyclooxygenase inhibitor; more particularly in combination with a selective inhibitor of the

inducible isoform of cyclooxygenase (COX-2). Thus, in a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in combination with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and inflammatory related disorders. And there is also provided a method of treating, or reducing the risk of, inflammation, inflammatory disease and inflammatory related disorders in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with a COX-2 inhibitor.

Particular compounds of the invention include:

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-3-pyridinecarbonitrile;

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chloro-benzonitrile;

(2*S*,4*R*)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol;

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile;

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-benzonitrile; and pharmaceutically acceptable salts thereof.

Unless otherwise indicated, the term "C1 to 4 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 4 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl.

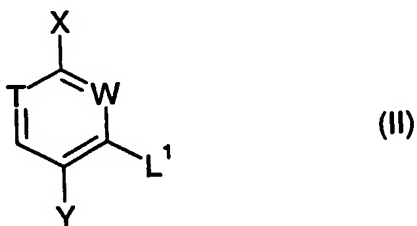
Unless otherwise indicated, the term "C1 to 4 alkoxy" referred to herein denotes a straight or branched chain alkoxy group having from 1 to 4 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluoro, chloro, bromo and iodo.

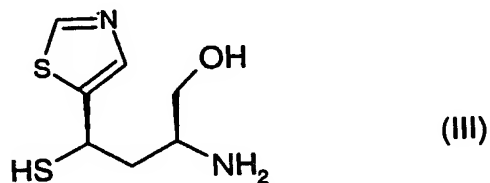
Examples of a "C1 to 4 alkyl or C1 to 4 alkoxy optionally further substituted by one or more fluorine atoms" include  $\text{CH}_2\text{F}$ ,  $\text{CHF}_2$ ,  $\text{CF}_3$ ,  $\text{CF}_3\text{CF}_2$ ,  $\text{CF}_3\text{CH}_2$ ,  $\text{CH}_2\text{FCH}_2$ ,  $\text{CH}_3\text{CF}_2$ ,  $\text{CF}_3\text{CH}_2\text{CH}_2$ ,  $\text{OCF}_3$  and  $\text{OCH}_2\text{CF}_3$ .

According to the invention, we further provide a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or racemate thereof which comprises:

(a) reaction of a compound of formula (II)

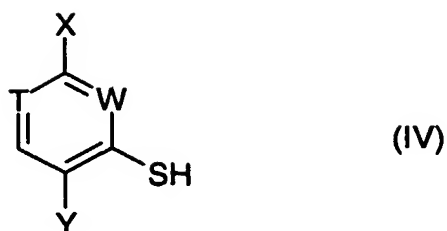


wherein T, X, Y and W are as defined in formula (I) and  $\text{L}^1$  represents a leaving group, with a compound of formula (III)

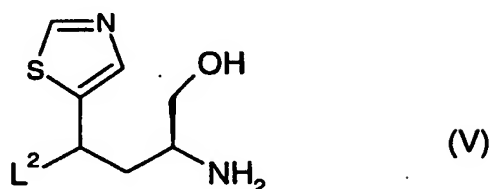


or

(b) reaction of a compound of formula (IV)



wherein T, W, X and Y are as defined in formula (I),  
with a compound of formula (V)



wherein  $L^2$  is a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a), the reaction is performed by treating a nucleophile of formula (III) with an electrophile of formula (II) in an inert solvent. Suitable leaving groups  $L^1$  include sulphonates and halides, particularly fluoride or chloride. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or caesium carbonate. Suitable organic solvents are those such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

In process (b), the reactants (IV) and (V) are coupled together in a suitable inert solvent such as tetrahydrofuran using, for example, Mitsunobu conditions. Thus, for example, the reactants are treated with a phosphine derivative and an azo derivative at a suitable temperature, generally between 0 °C and the boiling point of the solvent. Suitable

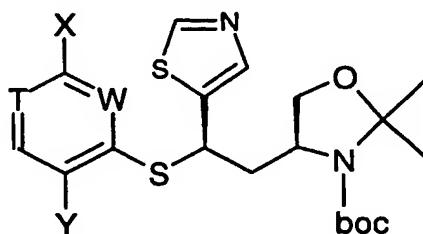
phosphine derivatives include triphenylphosphine and tributylphosphine. Suitable azo derivatives include diethyl azodicarboxylate, diisopropyl azodicarboxylate and 1,1'-(azodicarbonyl)dipiperidine. Suitable leaving groups  $L^2$  include hydroxy.

- 5 Alternatively in process (b), the reaction is performed by treating a nucleophile of formula (IV) with an electrophile of formula (V) in an inert solvent. Suitable leaving groups  $L^2$  include sulphonates and halides, particularly chloride or bromide. The reaction is generally performed in the presence of a non-nucleophilic base such as sodium hydride or caesium carbonate. Suitable organic solvents are those such as N,N-dimethylformamide,  
10 N-methyl-2-pyrrolidinone, tetrahydrofuran and dimethylsulfoxide. The reaction is generally conducted at a temperature between 0 °C and the boiling point of the solvent.

- It will be apparent to a person skilled in the art that in the above processes it may be desirable or necessary to protect an amine or hydroxyl or other potentially reactive group.  
15 Suitable protecting groups and details of processes for adding and removing such groups may be found by reference to the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

- In one preferred embodiment, amine groups are protected as carbamate derivatives, for  
20 example, as t-butyloxycarbamates.

In another particularly preferred embodiment, the amine and hydroxyl groups of compounds of formula (I) are protected simultaneously as a cyclic hemi-aminal as in formula (VI).



(VI)



Specific examples of the use of protecting groups are given in the Examples section.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

Salts of compounds of formula (I) may be formed by reacting the free base, or a salt, enantiomer or racemate thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, for example, water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed *in vacuo* or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

Intermediate compounds may be used as such or in protected form. Protecting groups and details of processes for their removal may be found by reference to the standard text "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The compounds of formula I may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

The compounds of formula (I) and their pharmaceutically acceptable salts are useful because they possess pharmacological activity in animals. In particular, the compounds are active as inhibitors of the enzyme nitric oxide synthase. More particularly, they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase and as such are predicted to be useful in therapy, for example, as anti-inflammatory agents. They may also have utility as inhibitors of the neuronal isoform of the enzyme nitric oxide synthase.

The compounds and their pharmaceutically acceptable salts are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part. In particular, the compounds are indicated for use in the treatment of inflammatory conditions in mammals including man.

Conditions that may be specifically mentioned are:

osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;

eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;

inflammatory eye conditions including uveitis, glaucoma and conjunctivitis;

lung disorders in which inflammation is involved, for example, asthma, bronchitis, chronic obstructive pulmonary disease, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome;

bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain,

meningitis and pancreatitis;

conditions of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable bowel syndrome, reflux oesophagitis, damage to the gastrointestinal tract resulting from infections by, for example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs; and other conditions associated with inflammation.

The compounds will also be useful in the treatment and alleviation of acute pain or persistent inflammatory pain or neuropathic pain or pain of a central origin.

We are particularly interested in the conditions inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease and pain.

The compounds of formula (I) and their pharmaceutically acceptable salts may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above. For example, the compounds may be useful in the treatment of atherosclerosis, cystic fibrosis, hypotension associated with septic and/or toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-term immunosuppression in organ transplant therapy, in the control of onset of diabetes, in the maintenance of pancreatic function in diabetes, in the treatment of vascular complications associated with diabetes and in co-therapy with cytokines, for example TNF or interleukins.

The compounds of formula (I) may also be useful in the treatment of hypoxia, for example in cases of cardiac arrest and stroke, neurodegenerative disorders including nerve degeneration and/or nerve necrosis in disorders such as ischaemia, hypoxia, hypoglycaemia, epilepsy, and in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia, for example pre-senile dementia, Alzheimer's disease and AIDS-related dementia, Sydenham's chorea, Parkinson's disease, Tourette's syndrome, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, muscular dystrophy, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, pain, autism, seasonal affective disorder, jet-lag, depression or other symptoms associated with premenstrual syndrome (PMS), anxiety and septic shock. Compounds of formula (I) may also be expected to show activity in the prevention and reversal of drug addiction or tolerance such as tolerance to opiates and diazepam, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders, cancer and in the induction of labour.

We are particularly interested in the conditions stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia, migraine, cancer, septic shock and pain.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, inhalation, intravenous, topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

According to the invention, we further provide a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX inhibitor, more particularly in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together  
5 within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The invention is illustrated, but in no way limited, by the following examples:

- 10 The following abbreviations are used:- DMSO (dimethylsulfoxide), DMF (*N,N*-dimethylformamide), THF (tetrahydrofuran), NMP (*N*-methylpyrrolidinone).

#### Example 1

- 15 2-[[*(1R,3S)*-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-3-pyridinecarbonitrile ethanedioate

- a) (4*S*)-4-[(2*R*)-2-Hydroxy-2-(2-chloro-5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester and (4*S*)-4-[(2*S*)-2-hydroxy-2-(2-chloro-5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester  
20

- n*-Butyl lithium (2.0M in hexanes, 21.6 ml) was added dropwise to a solution of 2-chlorothiazole (5.4 g) in THF (400 ml) at -78 °C under a nitrogen atmosphere. After 15 minutes a solution of (4*S*)-2,2-dimethyl-4-(2-oxoethyl)-3-oxazolidinecarboxylic acid,  
25 1,1-dimethylethyl ester (7.0 g) in THF (140 ml) was added dropwise and the reaction mixture was stirred for a further 60 minutes. The cooling was then removed and the mixture was stirred at room temperature for 60 minutes. The reaction mixture was poured into saturated aqueous ammonium chloride and the products extracted with diethyl ether. The combined extracts were washed with brine, dried (magnesium sulfate), filtered and

evaporated. Purification by chromatography (silica, 20% ethyl acetate/*iso*hexane as eluent) gave the (4*S*, 2*S*) sub-title compound (5.2 g) as a colourless oil.

MS APCI +ve  $m/z$  363  $[(M+H)^+]$ .

$^1H$  NMR 400MHz (DMSO- $d_6$ , 90°C) 7.49 (1H, s), 5.69 (1H, d), 4.85 (1H, dd), 3.96-3.86 (2H, m), 3.84-3.77 (1H, m), 2.10-1.99 (1H, m), 1.90 (1H, dt), 1.47 (3H, s), 1.40 (12H, s).

Further elution gave the (4*S*, 2*R*) sub-title compound (5.1 g, 42%) as a colourless oil.

MS APCI +ve  $m/z$  363  $[(M+H)^+]$ .

$^1H$  NMR 400MHz (DMSO- $d_6$ , 90°C) 7.49 (1H, s), 5.70 (1H, d), 4.92 (1H, apparent quin.), 4.05-3.98 (1H, m), 3.91-3.84 (2H, m), 2.16-2.07 (1H, m), 1.84 (1H, ddd), 1.48 (3H, s), 1.41 (12H, s).

b) (4*S*)-4-[(2*S*)-2-Hydroxy-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester

10% Palladium on charcoal was added to a solution of the (4*S*, 2*S*) product from Example 1 step (a) (5.2 g) and sodium acetate (2.9 g) in methanol (120 ml). The reaction mixture was stirred at 50 °C under 5 atmospheres of hydrogen for 16 h. The mixture was filtered and evaporated. The residue was then dissolved in dichloromethane, re-filtered and evaporated to give the sub-title compound (4.8 g) as a colourless oil.

MS APCI +ve  $m/z$  329  $[(M+H)^+]$ .

$^1H$  NMR 400MHz (DMSO- $d_6$ , 90°C) 8.90 (1H, d), 7.73 (1H, d), 5.49 (1H, d), 4.94 (1H, dt), 3.93-3.91 (2H, m), 3.85-3.78 (1H, m), 2.09 (1H, ddd), 1.94-1.89 (1H, m), 1.47 (3H, s), 1.41 (3H, s), 1.40 (9H, s).

c) (4*S*)-4-[(2*R*)-2-(Benzoylthio)-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of triphenylphosphine (7.9 g) in dry THF (100 ml) at 0 °C was added diisopropylazodicarboxylate (5.9 ml) dropwise over 5 minutes. After the addition was complete the mixture was stirred for 20 minutes and then a solution of the product from Example 1 step (b) (4.8 g) and thiobenzoic acid (3.5 ml) in THF (50 ml) was added. The cooling bath was removed and stirring continued at room temperature overnight. The

mixture was concentrated and the residue was purified by chromatography (silica, 10% diethyl ether/*isohexane* as eluent) to give the sub-title compound (4.4 g) as a yellow solid. MS APCI +ve  $m/z$  449 ( $[M+H]^+$ ).

5 d) (4*S*)-4-[(2*R*)-2-[(5-chloro-3-cyano-2-pyridinyl)thio]-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester

The product from Example 1 step (c) (290 mg) was treated with 7M ammonia in methanol (5 ml) and stirred at room temperature for 6 h. The solvent was evaporated, the residue dissolved in dry DMF (5 ml) and treated with 2,5-dichloro-3-pyridinecarbonitrile (112 mg) followed by cesium carbonate (210 mg) under nitrogen. The reaction mixture was stirred for 18 h, poured into brine and ethyl acetate and the organic layer separated, washed with water (2 x), brine and dried (magnesium sulfate). The solvent was evaporated and the residue purified by chromatography (silica, 25% ethyl acetate/dichloromethane as eluent) to give the sub-title compound (160 mg) as a viscous oil.

15 MS APCI +ve  $m/z$  481 ( $[M+H]^+$ ).

e) 2-[[1*R*,3*S*]-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-3-pyridinecarbonitrile ethanedioate

The product from Example 1 step (d) (160 mg) was stirred in 4M HCl in dioxane (1 ml) and methanol (1 ml) for 1 h. The reaction mixture was evaporated, azeotroped with diethyl ether (3 x), then treated with 1 equivalent of oxalic acid in ethanol (10 ml). The clear solution was treated with diethyl ether until complete precipitation and the solid collected by filtration, washed with diethyl ether and dried *in vacuo* at 40 °C for 2 h to give the title compound (60 mg) as a light brown solid.

25 MS APCI + ve  $m/z$  341 ( $[M+H]^+$ ).

$^1\text{H}$  NMR 400MHz (DMSO- $d_6$ ) 9.07 (1H, s), 8.87 (1H, d), 8.56 (1H, d), 8.07 (2H, bs), 8.00 (1H, s), 5.71 (1H, t), 3.57 (1H, dd), 3.49 (1H, dd), 3.12-3.04 (1H, m), 2.45-2.32 (2H, m).

Example 22-[[[(1R,3S)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chloro-benzonitrile dihydrochloridea) (4S)-4-[(2R)-2-[(5-Chloro-2-cyanophenyl)thio]-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester

The product from Example 1 step (c) (290 mg) was treated with 2-fluoro-4-chlorobenzonitrile (101 mg) and cesium carbonate (211 mg) according to the procedure of Example 1 step (d) to give the sub-title compound (160 mg) as a viscous oil.

MS APCI +ve  $m/z$  480 ( $[M+H]^+$ ).

b) 2-[[[(1R,3S)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chloro-benzonitrile dihydrochloride

The product of Example 2 step (a) was stirred in 4M HCl in dioxane (1 ml) and methanol (1 ml) for 1 h. The reaction mixture was evaporated, azeotroped with diethyl ether (3 x) and dried *in vacuo* at 40 °C for 2 h to give the title compound (113 mg) as a pale yellow solid.

MS APCI + ve  $m/z$  340 ( $[M+H]^+$ ).

$^1\text{H}$  NMR 400MHz (DMSO- $d_6$ ) 9.05 (1H, s), 8.15 (2H, bs), 7.86 (1H, d), 7.83 (1H, s), 7.81 (1H, d), 7.55 (1H, dd), 5.57 (1H, t), 3.59 (1H, dd), 3.51 (1H, dd), 3.07 (1H, br s), 2.31-2.23 (2H, m).

Example 3(2S,4R)-2-Amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol hydrochloridea) (4S)-4-[(2R)-2-[[2-Chloro-5-(trifluoromethyl)phenyl]thio]-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester



The product from Example 1 step (c) (190 mg) was treated with 4-chloro-3-fluorobenzotrifluoride (83 mg) and cesium carbonate (163 mg) according to the procedure of Example 1 step (d) to give the sub-title compound (105 mg) as a viscous oil.

MS APCI +ve  $m/z$  523 ( $[M+H]^+$ ).

5

b) (2S,4R)-2-Amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol hydrochloride

The product of Example 3 step (a) was reacted according to the procedure of Example 2 step (b) to give the title compound (58 mg) as a white solid containing the (2S, 4S) diastereomer as a 30% impurity.

10

MS APCI + ve  $m/z$  383 ( $[M+H]^+$ ).

$^1H$  NMR 300MHz (DMSO- $d_6$ ) 9.04 (1H, s), 8.15 (2H, br s), 7.86 (1H, d), 7.77-7.69 (2H, m), 7.61 (1H, s), 5.54 (1H, t), 3.63-3.55 (1H, m), 3.13-3.01 (2H, m), 2.34-2.19 (2H, m).

15

#### Example 4

2-[[[(1R,3S)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile dihydrochloride

20

a) (4S)-4-[[[(2R)-2-[[3-Cyano-6-(trifluoromethyl)-2-pyridinyl]thio]-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester

The product from Example 1 step (c) (190 mg) was treated with 2-chloro-6-trifluoromethyl-3-pyridinecarbonitrile (86 mg) and cesium carbonate (163 mg) according to the procedure of Example 1 step (d) to give the sub-title compound (117 mg) as a viscous oil.

25

MS APCI +ve  $m/z$  (515  $[M+H]^+$ ).

b) 2-[[[(1R,3S)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile dihydrochloride

30

The product of Example 4 step (a) was reacted according to the procedure of Example 2 step (b) to give the title compound (85 mg) as a white solid.

MS APCI + ve  $m/z$  (375  $[M+H]^+$ ).

$^1H$  NMR 300MHz (DMSO- $d_6$ ) 9.04 (1H, s), 8.57 (1H, d), 8.20 (2H, bs), 7.97 (1H, s), 7.89 (1H, d), 5.68 (1H, t), 3.60-3.56 (1H, m), 3.52 (1H, dd), 3.18-3.09 (1H, m), 2.48-2.41 (2H, m).

### Example 5

#### 2-[[[(1R,3S)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-benzonitrile dihydrochloride

##### a) (4S)-4-[(2R)-2-[(4-Chloro-2-cyanophenyl)thio]-2-(5-thiazolyl)ethyl]-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester

The product from Example 1 step (c) (190 mg) was treated with 5-chloro-2-fluorobenzonitrile (65 mg) and cesium carbonate (163 mg) according to the procedure of Example 1 step (d) to give the sub-title compound (160 mg) as a viscous oil.

MS APCI +ve  $m/z$  480 ( $[M+H]^+$ ).

##### b) 2-[[[(1R,3S)-3-Amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-benzonitrile dihydrochloride

The product of Example 5 step (a) was reacted according to the procedure of Example 2 step (b) to give the title compound (97 mg) as a pale yellow solid.

MS APCI + ve  $m/z$  340 ( $[M+H]^+$ ).

$^1H$  NMR 300MHz (DMSO  $d_6$ ) 9.04 (1H, s), 8.27 (2H, br s), 8.04 (1H, d), 7.81 (1H, s), 7.77-7.74 (2H, m), 5.58 (1H, t), 3.57 (1H, dd), 3.51 (1H, dd), 3.07-3.00 (1H, m), 2.27 (2H, t).

### Screens

The pharmacological activity of compounds according to the invention was tested in the following screens.

Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt thereof, may be screened for nitric oxide synthase inhibiting activity by a procedure based on that of Förstermann *et al.*, Eur. J. Pharm., 1992, **225**, 161-165. Nitric oxide synthase converts  $^3\text{H}$ -L-arginine into  $^3\text{H}$ -L-citrulline which can be separated by cation exchange chromatography and quantified by liquid scintillation counting.

Enzyme is prepared, after induction, from the cultured murine macrophage cell line J774A-1 (obtained from the laboratories of the Imperial Cancer Research Fund). J774A-1 cells are cultured in Dulbeccos Modified Eagles Medium (DMEM) supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 mg/ml streptomycin & 0.25 mg/ml amphotericin B). Cells are routinely grown in 225 cm<sup>3</sup> flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO<sub>2</sub>.

Nitric oxide synthase is produced by cells in response to interferon- $\gamma$  (IFN $\gamma$ ) and lipopolysaccharide (LPS). The medium from confluent culture flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 1 mg/ml LPS and 10 units/ml IFN $\gamma$ . After a period of 17-20 hours in culture, harvesting of cells is accomplished by scraping the cell sheet from the flask surface into the culture medium. Cells are collected by centrifugation (1000 g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20 °C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X-100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors comprising leupeptin (2 mg/ml), soya bean trypsin inhibitor (10 mg/ml), aprotinin (5 mg/ml) and phenylmethylsulphonyl fluoride (50 mg/ml).

For the assay, 25  $\mu\text{l}$  of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400  $\mu\text{M}$  NADPH, 20  $\mu\text{M}$  flavin adenine dinucleotide, 20  $\mu\text{M}$  flavin mononucleotide, 4  $\mu\text{M}$  tetrahydrobiopterin, 12  $\mu\text{M}$  L-arginine and 0.025 mCi L-[ $^3\text{H}$ ] arginine) is added to wells of a 96 well filter plate (0.45  $\mu\text{m}$  pore size) containing 25  $\mu\text{l}$  of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50  $\mu\text{l}$  of cell lysate (prepared as above) and

after incubation for 1 hour at room temperature is terminated by addition of 50 µl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 150 µl of a 25% aqueous slurry of Dowex 50W (Na<sup>+</sup> form) is added to the assay after which the whole is filtered into 96 well plates. 75 µl of filtrate is sampled and added to wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 µl sample which is increased to 1900 dpm in the reagent controls. Compound activity is expressed as IC<sub>50</sub> (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and aminoguanidine, which gives an IC<sub>50</sub> (50% inhibitory concentration) of 10 µM, is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained IC<sub>50</sub> values are calculated. Compounds that inhibit the enzyme by at least 25% at 100 µM are classed as being active and are subjected to at least one retest.

In the above screen, the compounds of Examples 1 to 5 were tested and gave IC<sub>50</sub> values of less than 10 µM indicating that they are expected to show useful therapeutic activity.

## Screen 2

Recombinant human NO synthases (iNOS, eNOS & nNOS) were expressed in *E. coli* and lysates were prepared in Hepes buffer (pH 7.4) containing co-factors (FAD, FMN, H<sub>4</sub>B), protease inhibitors, lysozyme and the detergent, CHAPS. These preparations were used, at suitable dilution, to assess inhibition of the various isoforms. Inhibition of NOS was determined by measuring the formation of L-[<sup>3</sup>H]citrulline from L-[<sup>3</sup>H]arginine using an adaptation of the method of Förstermann *et al.*<sup>9</sup> Enzyme assays were performed in the presence of 3 µM [<sup>3</sup>H]arginine, 1 mM NADPH and other co-factors required to support NOS activity (FAD, FMN, H<sub>4</sub>B, calmodulin, Ca<sup>2+</sup>). Since various NOS inhibitors have been reported to exhibit slow binding kinetics, or to inactivate the enzyme in a time

dependent manner, enzyme and inhibitor were pre-incubated for 60 min in the presence of NADPH before addition of arginine to initiate the reaction. Incubations continued for a further 60 min before the assays were quenched and [ $^3\text{H}$ ]citrulline separated from unreacted substrate by chromatography on Dowex-50W resin in a 96-well format.

5

In the above screen, the compounds of Examples 1 to 5 were tested and gave  $\text{IC}_{50}$  values of less than  $10\text{ }\mu\text{M}$  against the iNOS enzyme indicating that they are expected to show useful therapeutic activity.

10 Screen 3

Compounds also show activity against the human form of induced nitric oxide synthase as can be demonstrated in the following assay.

15 The human colorectal carcinoma cell line, DLD-1 (obtained from the European Collection of Animal Cell Culture - cell line number 90102540) was routinely grown in RPMI 1640 supplemented with 10%(v/v) foetal bovine serum, and 2mM L-glutamine, at  $37\text{ }^{\circ}\text{C}$  in 5%  $\text{CO}_2$ .

20 Nitric oxide synthase was induced in cells by addition of medium containing human recombinant gamma-IFN (1000 units/ml), TNF-alpha (200 U/ml), IL-6 (200 U/ml) and IL-1-beta (250 U/ml). After incubation for 18 hours at  $37\text{ }^{\circ}\text{C}$ , the medium was removed and the cells washed with warm phosphate buffered saline. Cells were incubated for a further 5 hours at  $37\text{ }^{\circ}\text{C}$  / 5%  $\text{CO}_2$  in RPMI 1640 containing  $100\mu\text{M}$  L-arginine and  $100\mu\text{M}$  verapamil-HCl in the presence and absence of test compounds.

25

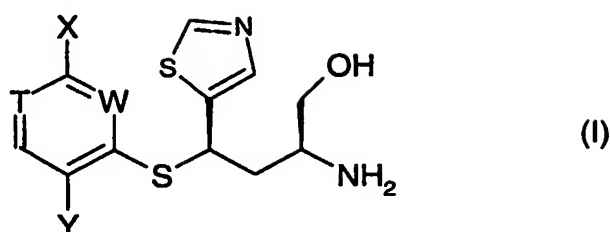
Nitrite accumulation was determined by mixing an equal volume of culture media with Griess reagent (10 mg/ml sulphanilamide, 1 mg *N*-(1-naphthyl)ethylenediamine in 1 ml 2.5% (v/v) phosphoric acid). Inhibition in the presence of compounds was calculated relative to the nitrite levels produced by untreated cells.  $\text{IC}_{50}$  values were estimated from a semi-log plot of % inhibition versus concentration of compound.

30

In this screen the compounds of Examples 1 to 5 gave  $IC_{50}$  values of less than 100  $\mu M$ , indicating that they are predicted to show useful therapeutic activity.

**CLAIMS:**

1. A compound of formula (I)



wherein:

T and W independently represent CR<sup>1</sup> or N; and when more than one R<sup>1</sup> group is present, each may be selected independently;

X and R<sup>1</sup> independently represent H, C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO<sub>2</sub>, CHO, COCH<sub>3</sub> or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms;

Y represents C1 to 4 alkyl, C1 to 4 alkoxy, halogen, CN, C≡CH, NO<sub>2</sub>, CHO, COCH<sub>3</sub> or NHCHO; said alkyl or alkoxy group being optionally further substituted by one or more fluorine atoms; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein Y represents CN or halogen.

3. A compound according to Claim 1 or 2 wherein X and R<sup>1</sup> independently represent H, halogen or CF<sub>3</sub>.

4. A compound of formula (I), according to Claim 1, which is:

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-3-pyridinecarbonitrile;

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chloro-benzonitrile;

(2*S*,4*R*)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol;

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-

pyridinecarbonitrile;

2-[[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chloro-benzonitrile;

or a pharmaceutically acceptable salt thereof.

5. A compound of formula (I), according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as a medicament.

6. A pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

7. The use of a compound of formula (I) according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

8. The use as claimed in Claim 7 wherein it is predominantly inducible nitric oxide synthase that is inhibited.

9. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

10. The use as claimed in Claim 9 wherein the disease is inflammatory bowel disease.

11. The use as claimed in Claim 9 wherein the disease is rheumatoid arthritis.



12. The use as claimed in Claim 9 wherein the disease is osteoarthritis.

13. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.

14. The use of a compound of formula (I) as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, in combination with a COX-2 inhibitor, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

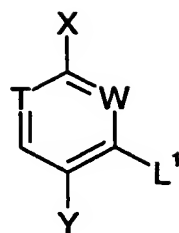
15. A method of treating, or reducing the risk of, human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, to a person suffering from, or at increased risk of, such diseases or conditions.

16. A method of treatment according to Claim 15 in which it is predominantly inducible nitric oxide synthase that is inhibited.

17. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof.

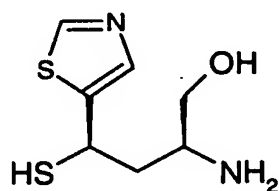
18. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable salt, enantiomer or racemate thereof, wherein the process comprises:

(a) reaction of a compound of formula (II)



(II)

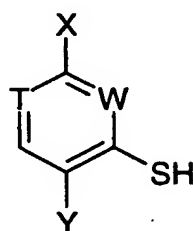
wherein T, X, Y and W are as defined in Claim 1 and L<sup>1</sup> represents a leaving group,  
with a compound of formula (III)



(III)

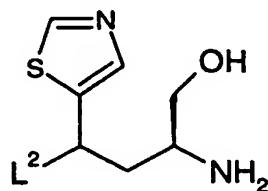
or

(b) reaction of a compound of formula (IV)



(IV)

wherein T, W, X and Y are as defined in Claim 1,  
with a compound of formula (V)



(V)

wherein L<sup>2</sup> is a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof; or converting one compound of formula (I) into another compound of formula (I); and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2003/001712

## A. CLASSIFICATION OF SUBJECT MATTER

C07D277/22, C07D277/24, C07D277/26, C07D277/28, C07D417/12, A61K31/426, A61P29/00, A61P19/02,  
**IPC7** A61P9/00, A61P25/06, A61P25/08, A61P25/18, A61P35/00, A61P37/08, A61P1/00, A61P31/12  
 According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, BIOSIS, EMBASE, MEDLINE, WPI DATA, EPO-INTERNAL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0162704 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.2001), See Example 53, page 63 and Example 79, page 95 --	1-18
A	WO 0162713 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.2001), See Example 43, page 62 --	1-18
A	WO 0162714 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.2001) --	1-18
A	WO 0162721 A1 (ASTRAZENECA AB), 30 August 2001 (30.08.2001) --	1-18

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

24 February 2004

Date of mailing of the international search report

27-02-2004

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**INTERNATIONAL SEARCH REPORT**

International application No.

**PCT/SE 2003/001712****C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p data-bbox="321 369 1084 432">WO 02090332 A2 (ASTRAZENECA AB), 14 November 2002 (14.11.2002)</p> <p data-bbox="651 464 773 506">-- -----</p>	1-18

# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT SE 2003/001712**

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **15-17**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see extra sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.  
**PCT SE 2003/001712**

**Box II.1**

Claims 15-17 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

## INTERNATIONAL SEARCH REPORT

24/12/2003

International application No.

PCT/SE 2003/001712

WO	0162704	A1	30/08/2001	AU	768364	B	11/12/2003
				AU	1043501	A	08/05/2001
				AU	3431501	A	03/09/2001
				BR	0108613	A	12/11/2002
				CA	2387643	A	03/05/2001
				CA	2397234	A	30/08/2001
				CN	1411435	T	16/04/2003
				EP	1229860	A,B	14/08/2002
				EP	1263711	A	11/12/2002
				GB	0004153	D	00/00/0000
				IL	150635	D	00/00/0000
				JP	2003512130	T	02/04/2003
				JP	2003523988	T	12/08/2003
				NO	20024014	A	25/09/2002
				US	2003158185	A	21/08/2003
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WO	0162713	A1	30/08/2001	AU	1043401	A	08/05/2001
				AU	3431301	A	03/09/2001
				CA	2387087	A	03/05/2001
				EP	1242914	A	25/09/2002
				EP	1263714	A	11/12/2002
				GB	0004149	D	00/00/0000
				JP	2003513365	T	08/04/2003
				JP	2003523992	T	12/08/2003
				US	2003105161	A	05/06/2003
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WO	0162714	A1	30/08/2001	AU	1153701	A	08/05/2001
				AU	3431401	A	03/09/2001
				EP	1263715	A	11/12/2002
				GB	0004152	D	00/00/0000
				JP	2003523993	T	12/08/2003
				US	2003065174	A	03/04/2003
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WO	0162721	A1	30/08/2001	AU	3260101	A	03/09/2001
				BR	0108539	A	22/10/2002
				CA	2388133	A	03/05/2001
				CA	2396960	A	30/08/2001
				CN	1404468	T	19/03/2003
				EP	1226631	A	31/07/2002
				EP	1263718	A	11/12/2002
				GB	0004151	D	00/00/0000
				IL	150640	D	00/00/0000
				JP	2003515234	T	22/04/2003
				JP	2003523995	T	12/08/2003
				NO	20024013	A	06/09/2002
				US	2003073685	A	17/04/2003
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WO	02090332	A2	14/11/2002	AU	7120001	A	21/01/2002
				NO	20034970	D	00/00/0000
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